Editorials

Osteoporosis at the End of the Century

DESPITE THE CURRENT PROMINENCE OF AIDS, osteoporosis may well be the disease of the 1990s. A recent report from the University of Southern California Gerontology Center ranked osteoporosis along with Alzheimer's disease as potential "budget busters."[1] Kelsey estimated that osteoporosis cost the nation $8 billion in 1986.[2] Even if disease prevalence in the elderly population remains constant, the rising number of elderly will raise that cost manyfold over the next few decades. More worrisome are data from several European sources that indicate an alarming rise in the age-adjusted incidence of hip fracture over the past 30 to 40 years.[3-5] Whether similar increases are occurring in the United States is uncertain. We were already close to the world leader in the incidence of hip fracture, and it may simply be that Europe is catching up to us. Either way, osteoporosis—particularly hip fracture—will strain our resources, both monetary and professional. Thus, it is useful that THE WESTERN JOURNAL OF MEDICINE has chosen to reprint in this issue a major current review of this disorder.[6]

Riggs emphasizes the traditional view that osteoporosis consists primarily of decreased bone mass. Indeed, that approach is explicit in the very name we give the disorder. The clinical problem, however, is most directly fragility, not porosity, and structures engineers recognize that fragility has many origins. A decreased quantity of material is only one of them. Arrangement and connectedness of the material—architecture—is another. Equally important is the loading history of the member, expressed in its accumulated burden of fatigue damage.

We all lose bone with age, and, indeed, by the usual age of hip fracture, virtually everyone is more than two standard deviations below the young adult mean. But not everyone fractures. Differences in a propensity to fall and in injury pattern are one reason. A growing body of evidence indicates convincingly that lost connectivity and excess fatigue damage are also important contributors to the fragility that we diagnose clinically as osteoporotic fracture.[7-9] Women with spine compression fractures have been found to have significantly less connectivity among their trabecular structures than do persons without fracture but with the same degree of lost mass. And studies of patients with hip fracture have shown local decreases in remodeling[9] so that fatigue damage accumulates specifically in the region of the femoral neck. The causes are not understood, but both abnormalities mean that the involved bone loses strength out of all proportion to its loss in mass. In brief, most of the low-trauma fractures we call osteoporotic appear to have at least two osseous parents. Reduced mass is only one of them.

The professional community has been slow to accept these facts, in part because of its investment in the notion of decreased mass, and in part because fragility itself is not easily detectable. Indeed, most of our research and all of our therapy is directed at altering bone mass and density. The ultrasound-based methods appear to have promise in detecting fragility directly,[10] but experience with them is still limited.

The effort directed at measuring and preventing bone loss has not, of course, been wasted. If it takes two fragility factors to result in low-trauma fracture, then preventing either will prevent the fracture. So maintaining optimal bone mass, where that is possible, remains a sound stratagem. But mass alone is clearly not enough, as the recent fluoride trial illustrated.[11] Recognizing that fragility has other definable causes helps to understand the clinical reality better and promises additional opportunities to intervene as well.

Unfortunately, while the struggle goes on to understand the disorder, the number of already fragile persons increases yearly. Even if a magic bullet were discovered today, we are certain to reap a bumper crop of fractures whose seeds have long since been sown. A few simple stratagems—simple in concept if not equally easy to implement—may help mitigate this growing problem.

Most fractures are caused by trauma, even the fragility fractures that are associated with osteoporosis. Preventing falls is a sensible approach for the already fragile elderly. Another is dissipating the force of injury by soft tissue or other shock-absorbing material. Drop a glass tumbler on a concrete floor and it invariably shatters. With even a relatively thin carpet, it will usually bounce. Hip fracture is unusual in overweight persons, in part because the bone is stronger, but in part also because it is better padded. If we cannot pad our elderly, perhaps their environments can be padded.

Adequate nutrition is one potentially controllable factor contributing directly to bone strength or fragility. Hip fracture is more common and heals less well in those who are malnourished. A recent report from Geneva underscores the importance of paying attention to nutritional factors even in persons who have already suffered a fracture.[12] A related concern is the importance of adequate calcium intake in maintaining maximal bone mass as we age. Several studies now show that hip fractures are substantially less common in persons with high calcium intakes,[13,14] and even thiazide use—presumably through its calcium-sparing effect—is associated with reduced hip fracture risk.[15]

One of the recommendations of the 1984 National Institutes of Health Consensus Conference on osteoporosis was that postmenopausal women should receive calcium intakes of 1,500 mg per day.[16] This recommendation remains sound and certainly is better supported by scientific evidence today than it was then. Even 1,500 mg may not be enough for everyone, since absorption efficiency falls with age and since, with reduced solar exposure among the elderly, vitamin D status is commonly marginal or inadequate. It must be stressed that the reduced bone mass that is one of the contributors to osteoporotic fragility has many causes, just as does the reduced hemoglobin mass of anemia. Low calcium intake is only one of them, as iron deficiency is only one of the causes of anemia. But in both cases, it is a cause that something can be done about. It would not be realistic to expect that assuring an adequate calcium intake will prevent all age-related bone loss. Fortunately, our goal can be more modest: to prevent any calcium deficiency component of that loss.

There has been unfortunate confusion around this issue of calcium intake, largely because a high calcium intake does not prevent the loss of bone that occurs in the immediate postmenopause.[17] This loss is due specifically to estrogen withdrawal. In just the same way, calcium will not prevent a

loss of bone due to immobilization. Nevertheless, calcium supplements *will* prevent the loss of bone due to inadequate calcium intake. Our mistake has been to generalize from studies in the immediate postmenopause, which is dominated by the readjustments produced by estrogen withdrawal, to periods either earlier or later, for which there is ample evidence that a high calcium intake is bone sparing.[18-20]

Although it is never too late to start to assure an adequate calcium intake, it must also be acknowledged that the roots of the problem go deep. The building of an optimal bone mass, particularly during the teen years and young adulthood, is of critical importance. Many teenaged girls today have such low calcium intakes[21] that there is no possibility that they can repeal the law of the conservation of mass and make much of a skeleton from the raw materials they provide their bodies. It is today's teenagers with low calcium intakes who are likely to be our hip fracture patients in 60-plus years from now. We are doomed to a perpetual game of catch-up until we can implement effective populationwide strategies to increase the level of calcium intake. This is an achievable goal, just as years ago ways were found to increase intakes of such trace nutrients as fluoride and iodine. If one is tempted to think about this as medicating the population, it may be instructive to bear two facts in mind: the primitive human calcium intake—the one, presumably, to which our physiology is adapted—is well in excess of 1,500 mg per day[22]; and the natural food sources of our closest primate relatives provide them with diets containing roughly four times the calcium nutrient density of a typical first-world human diet.

Next, there is the importance of maintaining physical activity, both before and after a fracture. Our skeletons are, after all, mechanical systems, and the principal intrinsic stimulus to their self-maintenance is mechanical loading. Not only does physical activity help preserve bone mass, but it probably is an important factor in the maintenance of adequate remodeling, without which fatigue damage will accumulate. It is difficult to increase bone mass very much by increasing physical activity; unfortunately, it is easy to lose mass with inactivity. So maintaining load-bearing activity is critical.

Finally, a brief word about pharmacotherapy. Recent promising reports describing the use of bisphosphonates indicate that these agents may have a useful role in the management of patients who already have the disorder.[23,24] Many years of experience have been accumulated with their use in Paget's disease, and so their long-term safety is reasonably assured. They are, however, remodeling suppressors, and their long-term effects in persons who already have compromised skeletal strength will have to await further study.

Fluoride is another issue. Riggs is cautious, which is understandable, given his recently reported experience in which fluoride did not decrease fracture incidence despite a nearly 40% increase in bone mass.[11] The protocol for his study, however, dictated not by the investigators but by the sponsoring agency, called both for what is now recognized to be a toxic dose of fluoride and for administration in a form that is known to produce excess gastrointestinal irritation.[25] The high peak blood concentrations produced by such therapy may well produce a degree of osteoblast toxicity that lower, but more sustained, blood levels do not. Certainly they will produce areas of hypercrystallinity in newly deposited bone mineral that will result in bone of different mechanical properties from bone mineralized out of a medium with a lower fluoride concentration. Fluoride is now approved for the treatment of osteoporosis in at least eight European countries and should not yet be counted out of the running in the US.

ROBERT P. HEANEY, MD
John A. Creighton University Professor
Creighton University
Omaha, Nebraska

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Nitric Oxide, Nitrovasodilators, and L-Arginine—An Unusual Relationship

CERTAINLY ONE OF THE MOST interesting and potentially far-reaching discoveries that has taken shape over the past few years concerns a novel mammalian pathway that leads to the formation of nitric oxide from the amino acid L-arginine.[1] This unusual biochemical pathway brought together seemingly unrelated fields of research. Nitric oxide formation has now been found in a number of cell types, but the first and, until now, the most thorough characterizations have been in macrophages, endothelial cells, and cells of the central ner-